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10/714,228	11/14/2003	Luigi Grasso	MOR-0251	4529

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,228	GRASSO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-68 is/are pending in the application.

4a) Of the above claim(s) 102-134,137 and 138 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 62-101,135 and 136 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/25/04 8/04/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: IDS 5/1/2007.

DETAILED ACTION

Acknowledgement is made of applicants election with traverse of Group IV. The traversal is on the group that the restriction is improper because it would not be undue burden to search Groups V and VI with the claims of Group IV. Applicant maintains that a search for Group IV would necessarily lead to the subject matter of Groups V and VI. This has been considered and found persuasive. Groups V and VI are rejoined to Group IV for examination at this time.

Claims 1-68 are pending. Claims 102-134, 137 and 138, drawn to non-elected inventions are withdrawn from consideration. Claims 62-101, 135 and 136 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62-101, 135 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 62, 81, 91 recite high affinity antibodies. The term "high affinity" in claims 62, 81 and 91 is a relative term which renders the claim indefinite. The term "high affinity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. .

Claim 66, 70, 73, 78, 81, 85, 87, 91, 96, 99 recite "titer" in relation to the antibodies produced from hybridoma cells. It is unclear what the term "titer" means in this context. The art teaches that "titer" is defined as a measure of the amount of antibody in an antiserum per unit volume of original serum (Herbert et al, Dictionary of Immunology, 1985, page 221). The instant claims do not entail and original antiserum, thus the metes and the bounds of claims requiring an altered "titer" are unclear. For purpose of examination, and increased antibody

affinity will be read as correlating with an increased antibody titer. This interpretation is supported by section f of claims 81 and 91.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 72, 80, 89, 90, 100 and 101 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharon (PNAS, 1990, Vol. 87, pp. 4814-4817).

Claim 72 is drawn to an antibody produced by a hybridoma cell of claim 71. Claim 80 is drawn to an antibody produced by a hybridoma of claim 79. Claim 89 is drawn to a mammalian expression cell produced by the method of claim 81, 85, or 88. Claim 90 is drawn to an antibody produced by a mammalian expression cell of claim 89. Claim 100 is drawn to a mammalian expression cell produced by the method of claim 91, 95, 96, or 97. Claim 101 is drawn to an antibody produced by a mammalian expression cell of claim 100.

Sharon discloses a hybridoma expressing an antibody having a 200-fold increase in affinity after oligonucleotide-directed mutagenesis (page 4816, second column , second full paragraph). Sharon discloses that DNA from the oligonucleotide-directed mutagenesis was transfected into the H-chain loss cell line to form transfectomas which are mammalian expression cells. The instant claims are product by process claims; The M.P.E.P. (2113) states

> PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS
>
> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable

even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The hybridomas and the high affinity antibodies disclosed by Sharon meet the limitations of the claims because the hybridomas are mammalian expression cells and because the high affinity antibodies produced therefrom are the same as that claimed.

Claims 71, 72, 79, 80, 89, 90, 100 and 101 are rejected under 35 U.S.C. 102(b) as being anticipated by Yelton et al (Journal of Immunology, 1995, Vol. 155, pp. 1994-2004).

Claim 71 is drawn to a hybridoma cell produced by the method of claim 62, 66, 67, or 68. Claim 79 is drawn to a hybridoma cell produced by the method of claim 73 or 77.

Yelton et al disclose a high affinity Br96 anti-carcinoma antibody expressed by a recombinant hybridoma cell (page 1996, under the heading of "Generation of mutants in mammalian cells") which fulfills the limitation of a mammalian expression cell. Claims 89, 90, 100 and 101 are product-by-process claims and are rejected because the mammalian expression cells and antibodies of the prior art anticipate the instant antibodies and hybridoma cells regardless of the method of production.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62-101, 135 and 136 are rejected under 35 U.S.C. 103(a) as being obvious over Borrebaeck (Adv Drug Delivery Reviews, 1988, Vol. 2, pp. 143-165) in view of Yelton et al (Journal of Immunology, 1995, Vol. 155, pp. 1994-2004), Zan et al (Immunity, 2001, Vol. 14, pp. 643-653) and Nicolaides et al (WO02/054856).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 62 is drawn to a method for producing hybridoma cells producing high-affinity antibodies from in vitro immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen in vitro; (b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells; (c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells; (d) performing a screen for binding of antibodies to antigen for antibodies produced from said hypermutated hybridoma cells; and (e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells;

thereby producing hybridoma cells producing high-affinity antibodies. Claim 63 embodies the method of claim 62 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein. Claim 64 embodies the method of claim 62 wherein said inhibitor is an anthracene having various substitutions for the ring hydrogens. Clam 65 specifies alternative functional groups on R1 to R10 of the anthracene of claim 63. Claim 66 embodies the method of claim 62 further comprising a screen for hypermutated hybridomas that also produce antibodies in higher titers than said parental hybridomas. Claim 67 embodies the method of claim 62 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma. Claim 68 embodies the method of claim 66 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma. Claim 69 embodies the method of claim 62 wherein said high affinity antibodies have an affinity of at least about $10^{7} M.^{-1}$ to about $10^{14} M.^{-1}$. Claim 70 embodies the method of claim 66 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

Claim 73 is drawn to a method for producing hybridoma cells that produce high titers of antibodies from in vitro immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen in vitro; (b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells; (c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells; (d) performing a screen of said hypermutated hybridoma cells for antigen-specific antibodies produced in higher titers than that produced by said parental hybridoma cells; and (e) selecting hypermutated hybridoma cells that produce higher titers of antibodies than that produced by said parental hybridoma cells; thereby producing hybridoma cells that produce high titers of antibodies. Claim 74 embodies the method of claim 73 wherein said chemical inhibitor is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference

molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein. Claim 75 specifies alternative functional groups on R1 to R10 of the anthracene of claim 74. Claim 76 embodies the method of claim 75 wherein $R._1$-$R._{10}$ are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl. Claim 77 embodies the method of claim 73 further comprising the step of removing said chemical inhibitor from said growth medium following hypermutation, thereby stabilizing the genome of said hypermutated hybridoma. Claim 78 embodies the method of claim 73 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

Claim 81 is drawn to a method for producing mammalian expression cells that produce high titers of high-affinity antibodies from in vitro immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen in vitro; (b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells; (c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen; (d) cloning immunoglobulin genes from said hybridoma into a mammalian expression cell; (e) incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair; (f) performing a screen for mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells; thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from in vitro immunized immunoglobulin-producing cells. Claim 82 embodies the method of claim 81 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

Claim 83 specifies alternative functional groups on R1 to R10 of the anthracene of claim 74. Claim 84 embodies the method of claim 83 wherein $R._1$-$R._{10}$ are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

Claim 84 embodies the method of claim 83 wherein R.sub.1-R.sub.10 are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl. Claim 85 embodies the method of claim 81 further comprising screening for hypermutated hybridomas that also produce antibodies in higher titers than said parental hybridomas, prior to collection of said antibodies from said hypermutated hybridoma cells,. Claim 86 embodies the method of claim 81 wherein said high affinity antibodies have an affinity of at least about 10^{7} M.$^{-1}$ to about 10.^{14} M.$^{-1}$. Claim 87 embodies the method of claim 81 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell. Claim 88 embodies the method of claim 81 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated mammalian expression cells.

Claim 91 is drawn to a method for producing mammalian expression cells that produce high titers of high affinity antibodies to a selected antigen from in vitro immunized immunoglobulin-producing cells comprising: (a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen in vitro; (b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells; (c) incubating said hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells; (d) performing a screen for binding of antigen for antibodies produced from said hypermutated hybridoma cells; (e) selecting hypermutated hybridoma cells that produce antibodies with greater affinity for said antigen than antibodies produced by said parental hybridoma cells; (f) cloning immunoglobulin genes from said hypermutated hybridoma cells into a mammalian expression cell, thereby forming parental mammalian expression cells; thereby producing mammalian expression cells that produce high titers of high-affinity antibodies from in vitro immunized immunoglobulin-producing cells. Claim 92 embodies the method of claim 91 wherein said chemical inhibitor of mismatch repair is selected from the group consisting of an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor and an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein. Claim 93 specifies alternative functional groups on R1 to R10 of the anthracene of claim 74. Claim 94 embodies the method of claim 92 wherein $R._{1}$-$R._{10}$ are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl or hydroxybutyl. Claim 95 embodies the method of claim 91 wherein said high affinity antibodies have an affinity of at least about 1.times.10.sup.7 M.sup.-1 to about 1.times.10.sup.14 M.sup.-1. Claim 96 embodies the method of claim 91 further comprising the steps of: incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair, thereby forming a hypermutated mammalian expression cell; and screening for hypermutated mammalian expression cells that produce a higher titer of antibodies that said parental mammalian expression cells.
Claim 97 embodies the method of claim 91 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated hybridoma cells. Claim 98 embodies the method of claim 96 further comprising removing said chemical inhibitor, thereby stabilizing the genome of said hypermutated mammalian expression cells. Claim 99 embodies the method of claim 96 wherein said higher titer of said antibodies is at least about 1.5-8 fold greater that the titer produced by said parental hybridoma cell.

Claim 135 embodies a method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence encoding a protein selected from the group consisting of SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:6; SEQ ID NO:8; SEQ ID NO:10; SEQ ID NO:12; SEQ ID NO:14; SEQ ID NO:16; SEQ ID NO:18; SEQ ID NO:20; SEQ ID NO:22; SEQ ID NO:24; SEQ ID NO:26; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:32; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:38; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; and SEQ ID NO:50.

Claim 36 is drawn to a method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; SEQ ID NO:21; SEQ ID NO:23; SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; and SEQ ID NO:49.

Borrebaeck et al teach in vitro immunization and the production of hybridomas thereby (pages 145-146). Borrebaeck et al teach that high affinity antibodies are obtained only when lose doses of antigens are used in vitro (pp. 150-151, under the heading of "Affinity"). Borrebaeck et al suggests that it would be useful to be able to obtain antibodies from in vitro immunization having affinities greater than 10^9 M^{-1} (page 151-151 under the heading of "Future Developments").

Yelton et al teach that increasing antibody affinity 10-fold provides a 2.5 to 3.0-fold therapeutic advantage in anti-tumor activities (page 2002, second column, lines 8-13 and lines 19-23). Yelton et al teach the cloning of hybridoma DNA into a cell expression system using codon based mutagenesis and the selection of higher affinity antibodies produced from the expression of the mutated hybridoma antibody genes (page 1995, Figure 1).

Zan et al (Immunity, 2001, Vol. 14, pp. 643-653) teach that B cell contain trans-lesion polymerases that include error prone polymerases (mis-pair inserters) and polymerases able to extend DNA chains from a mis-pair page 643, second column, second full paragraph to page 644, first column, line 22).

Nicolaides et al teach the use of chemical inhibitors of mis-match repair to make hypermutable cells. Nicolaides et al teach that the use of said chemical inhibitors is more efficient than relaying on natural mutation rates (abstract). Nicolaides et al teach chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, nuclease inhibitor, RNA interference molecule, a polymerase inhibitor or an anti-sense oligonucleotide that specifically hybridizes to a nucleotide encoding a mis-match repair protein (page 10, lines 19-25). Nicolaides et al teach the cDNA encoding the mis-match repair proteins of SEQ ID NO: 14 (mouse PMS2), SEQ ID NO:16 (human PMS2), SEQ ID NO:18 (PMS1), SEQ ID NO:20 MSH2), SEQ ID NO:22 (MLH1), SEQ ID NO:24 (hPMS2), SEQ ID NO:26 (GTBP) and SEQ ID NO:28 (MSH3) (pp. 40-66) which fulfill the specific limitations of claims 135 and 136. Nicolaides et al teach that an example of a host cell which can become hypermutable by treatment with the chemical inhibitors of the invention include human, mammalian and rodent cells (page 14, lines 1-3). Nicolaides et al teach the transient exposure of cells to the chemical inhibitor allowing for stabilization of the genome (page 10, lines 14-19) which fulfills the specific embodiment of claims requiring the stabilization of the genome.

It would have been prima facie obvious at the time the claimed invention was made to transiently expose hybridoma cells formed from in vitro immunized lymphocytes to chemical inhibitors of mis-match repair as taught by Nicolaides et al in order to mimic affinity maturation in vivo and obtain higher affinity antibodies and thus higher titer antibodies. One of skill in the art would have been motivated to do so by the teachings of both Borrebaeck et al and Yelton et al on the desirability of exploiting in vitro immunized antibodies to obtain high affinity antibodies; and the teachings of Nicolaides et al on the chemical inhibitors of mismatch repair for inducing cells including mammalian cells to become hypermutable and the teachings of Zan et al on the ability of B cells to induce somatic mutations therein by by-pass polymerases allowing for insertion of mutations and extension of DNA chains from the mutation. One of skill in the art would understand that the inhibitors of Nicolaides et al would increase the rate of mutations inserted by the by-pass polymerases and thus provide for a higher rate of somatic mutations and the accumulation of a population of somatic mutants allowing for the selection of higher affinity antibodies formed as a result of said somatic mutation.

It would also have been obvious to clone the un-mutated genes from the hybridoma into a expression construct as taught by Yelton et al and expose said construct to chemical inhibitors of mismatch repair in place of codon–based mutagenesis. One of skill in the art would have been motivated to do so because the use of the chemical inhibitors is more efficient and less time consuming especially in the case of the anthracenes, thereby allowing for the screening of more hybridomas.

One of skill in the art would also have been motivated to select antibodies with an affinity of greater than 10^9 M^{-1} as taught by Borrebaeck et al and therefore fulfills the limitations of claims 69, 86 and 95.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 72, 80, 90 and 101 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 20 of copending Application No. 10/243,130. Although the conflicting claims are not identical, they are not patentably distinct from each other because the antibody of the '130 application can anticipate the instant claims because the instant claimed antibody is not limited by the method of producing said antibody..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella, Ph.D./
Primary Examiner
Art Unit 1643